In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

* *		
NICOLETTE MCGUIRE,	*	
	*	No. 10-609V
Petitioner,	*	Special Master
	*	Christian J. Moran
	*	
v.	*	Filed: September 18, 2015
	*	
SECRETARY OF HEALTH	*	Entitlement; human
AND HUMAN SERVICES,	*	papillomavirus ("HPV")
	*	vaccine; headaches; cytokines.
Respondent.	*	
* *		

Ronald C. Homer, Sylvia Chin-Caplan, and Meredith Daniels, Conway, Homer & Chin-Caplan, P.C., Boston, MA, for Petitioner;
Debra A. Filteau Begley, U. S. Dep't of Justice, Washington, DC, for Respondent.

PUBLISHED DECISION DENYING COMPENSATION[1]

Nicolette McGuire alleges that the human papillomavirus vaccinations she received when she was 20 years old caused her to develop headaches, resulting in great pain. Ms. McGuire seeks compensation pursuant to the National Childhood Vaccine Injury Compensation Program, codified at 42 U.S.C. § 300aa–10 through 34 (2012).

To support her claim, Ms. McGuire filed her medical records. Because the records were inconsistent about when Ms. McGuire started having significant headaches after the vaccination, she provided her recollections during a hearing

[1] The E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (Dec. 17, 2002), requires that the Court post this decision on its website. Pursuant to Vaccine Rule 18(b), the parties have 14 days to file a motion proposing redaction of medical information or other information described in 42 U.S.C. § 300aa-12(d)(4). Any redactions ordered by the special master will appear in the document posted on the website.

held on November 4, 2011. Revised Findings of Fact, issued October 12, 2012, determined that Ms. McGuire started experiencing prolonged headaches on October 25-28, 2007, and these headaches became constant approximately one week later.[2]

After the Revised Findings of Fact were issued, the parties presented opinions from experts retained for the litigation. In due course, a hearing was held during which the four experts testified.

The undersigned has considered the entire record. After weighing the evidence, the undersigned finds that Ms. McGuire has not met her burden of establishing that the HPV vaccination caused her headaches. The simplest explanation is that Ms. McGuire failed to present a reliable basis for concluding, on a more-likely-than-not basis, that the HPV vaccination can cause headaches that last for months and years.

The remainder of the decision elaborates on this basic finding. The background of the experts are set forth initially because their experience provides a context for understanding Ms. McGuire's medical history, which is set forth in the following section. Collectively, those sections are the foundation for the analysis section that explains why the evidence does not preponderate in Ms. McGuire's favor.

Biographies

The parties rely upon the doctors whom they retained as expert witnesses to explain the respective positions regarding Ms. McGuire's illness. Ms. McGuire retained Dr. Spencer Weig, an expert in child neurology, and Dr. Sahar Swidan, a PharmD who specializes in headache treatment. The Secretary retained Dr. David

[2] The parties disagreed, for a time, about the type of headache Ms. McGuire suffered. Ms. McGuire proposed chronic daily headaches (CDH) and the Secretary proposed new daily persistent headaches (NDPH). However, before the hearing, the parties concluded that classifying Ms. McGuire's headaches as either CDH or NDPH would not affect the outcome of the claim that the HPV vaccination caused Ms. McGuire's headaches. Resp't's Status Rep., filed Mar. 11, 2015.

Alexander, a neurologist, and Dr. Andrew Saxon, an immunologist.[3] The following sections provide some context for the opinions discussed throughout this decision.

Dr. Weig

Background. After completing his education in medical school in 1983, Dr. Weig practiced pediatric neurology from 1987-2011. Tr. 174. His patients were younger than 19 years old. Tr. 168. If a potential patient were older than 20 years, Dr. Weig referred the person to an adult neurologist. Tr. 209.

Dr. Weig treated children with a variety of neurologic disorders. Some of these disorders, such as acute disseminated encephalomyelitis, limbic encephalitis, NDA receptor encephalitis, multiple sclerosis, transverse myelitis, acute inflammatory demyelinating polyneuropathy or Guillain-Barré Syndrome, chronic inflammatory demyelinating polyneuropathy, dermatomyositis, and myasthenia gravis, involve the immune system. Tr. 173; exhibit 30 (Dr. Weig's report) at 5-6. For these patients, he sometimes, but not always, consulted a colleague who specialized in immunology. Tr. 212. His knowledge of how diseases originate was an essential part of his ability to practice as a pediatric neurologist. Tr. 176.

In Dr. Weig's practice, approximately one-third of his patients suffered from some type of headache. Tr. 148-49. For CDH, Dr. Weig cared for 20-30 people in his practice and more during hospital rounds. Tr. 271-72. For NPDH, Dr. Weig estimated that he saw two or three people who satisfied the formal diagnostic criteria. Tr. 210. He most recently saw a patient suffering from CDH in May 2011, shortly before he retired. Tr. 277.

Although Dr. Weig retired from practicing pediatric neurology, he has continued his teaching duties, which began in 1990. Currently, he advises medical school students during rounds at a hospital. Tr. 148, 276. He does not see any patients outside of hospital rounds. Tr. 275. To maintain his license, he attends conferences with other doctors approximately twice per month. Annually, he spends about 20-30 hours at these conferences. Tr. 276.

[3] The Secretary retained Dr. Saxon after her original immunologist, Burton Zweiman, died. Resp't's Status Rep., filed Jan. 2, 2014. At the Secretary's suggestion, Dr. Zweiman's report and curriculum vitae were struck from the record. Order, issued Mar. 6, 2015.

Dr. Weig's education, training, and experience qualified him as an expert in pediatric neurology. Tr. 175-76. However, the Secretary raised two arguments about Dr. Weig's experience that reduced the value of his opinion. The lesser point is Dr. Weig's background as a pediatric neurologist does not perfectly fit Ms. McGuire's case because her headaches began when she was 20 years old. Tr. 165-70. Special masters have sometimes found the differences between pediatric neurology and adult neurology to be significant. See, e.g., Milik v. Sec'y of Health & Human Servs., No. 01-64V, 2014 WL 6488735, at *12 (Fed. Cl. Spec. Mstr. Oct. 29, 2014) (crediting a pediatric neurologist's opinion regarding childhood developmental delays), mot. for rev. denied, 121 Fed. Cl. 68 (Fed. Cl. Apr. 29, 2015); Deribeaux v. Sec'y of Health & Human Servs., No. 05-306V, 2011 WL 6935504, at *38 (Fed. Cl. Spec. Mstr. Dec. 9, 2011) (crediting a pediatric neurologist's interpretation of an MRI performed on a child), mot. for rev. denied, 105 Fed. Cl. 583 (Fed. Cl. 2012), aff'd, 717 F.3d 1363 (Fed. Cir. 2013). However, the Secretary did not present any evidence, such as testimony from the neurologist that she retained, that established CDH in the pediatric population differs from CDH in the adult population. Thus, despite his pediatric focus, Dr. Weig's opinion remains relevant. See Hall v. Sec'y of Health & Human Servs., No. 02-1052V, 2009 WL 3423036, at *30 (Fed. Cl. Spec. Mstr. Oct. 6, 2009) (stating, in the context of awarding attorneys' fees and costs, that "the fact that someone else may have better qualifications does not mean that [a retained doctor] was entirely unqualified"); cf. Sullivan v. Sec'y of Health & Human Servs., No. 10-398V, 2015 WL 1404957, at *20 (Fed. Cl. Spec. Mstr. Feb. 13, 2015) (stating "the possibility of a better study is not an effective critique of an existing, otherwise valid study").

The Secretary's second criticism of Dr. Weig is more meaningful. The Secretary argued that Dr. Weig lacked the training in immunology to offer a theory of how the HPV vaccine causes CDH via the immune system. Tr. 171-73. Dr. Weig admitted that his formal training in immunology came in medical school from which he graduated in 1973. Tr. 145-46, 172. He is not board-certified in immunology. Tr. 149-50. In addition, after Dr. Weig presented his first report and the Secretary countered with a neurologist plus an immunologist (first Dr. Zweiman, then Dr. Saxon), Ms. McGuire announced a plan to retain an immunologist to support Dr. Weig.[4]

[4] Ms. McGuire did not present testimony from an actual immunologist. She presented testimony from Dr. Swidan, whose qualifications are reviewed below.

Although Dr. Weig's working knowledge of immunology suffices as a basis to explain a general theory, Dr. Weig lacked any detailed understanding of immunology. For example, Dr. Weig's knowledge of the function and working of cytokines was limited. He was unable to discuss how cytokines like tumor necrosis factor alpha ("TNF") are produced, stating instead that he would have to defer to an immunologist. Tr. 279. Dr. Weig's lack of specialization in immunology makes his opinion on immunologic topics less valuable than the opinion of Dr. Saxon, who is an immunologist. Locane v. Sec'y of Health & Human Servs., 685 F.3d 1375, 1380 (Fed. Cir. 2012) (finding that special master was not arbitrary in considering the backgrounds of experts and crediting the expert with a more specific specialization).

Opinion. Dr. Weig expressed his opinions in four reports. Exhibits 28, 30, 37, and 40. He categorized Ms. McGuire's headaches as chronic daily headaches. He opined that the HPV vaccine can cause CDH by stimulating the production of cytokines, particularly TNF. For this proposition, he relied primarily upon a paper whose lead author is Ligia Pinto. Dr. Weig also opined that increased levels of TNF contribute to the pathology of CDH and for this proposition, Dr. Weig primarily relied upon a paper co-written by Todd Rozen and Sahar Swidan. In his January 12, 2015 report, Dr. Weig expressed the opinion that expected interval between vaccination and the onset of headaches is 5 days to 6 weeks. Dr. Weig also defended Dr. Swidan's qualifications.

Dr. Alexander

Background. Dr. Alexander completed medical school in 1979, and a residency in neurology in 1983. Exhibit A, tab 1 (C.V. of Dr. Alexander). In 1984, he started private practice in Los Angeles, California. He started teaching at UCLA in 2002, and became a full-time professor there in 2008. Tr. 304-06. He holds board-certifications in three areas: neurology, spinal cord medicine, and strokes. Tr. 306.

As a practicing neurologist, he has treated hundreds of patients with CDH. Tr. 414. However, he has not diagnosed any patient with the rare form of CDH, NDPH. Tr. 310, 404.

His current responsibilities include three duties. He treats patients at a hospital with 11 beds.[5] Very few of his current patients suffer from CDH. Tr. 309. He teaches neurologic topics, particularly disorders of the spinal cord and strokes. Tr. 313. He also has administrative responsibilities, including serving on one of UCLA's institutional review boards, which authorizes research projects involving human beings. Tr. 311.

The Secretary requested that Dr. Alexander be recognized as an expert in adult neurology. Ms. McGuire did not object. Tr. 314-15.

Although Dr. Alexander qualifies as an expert in neurology, his background does not match the subject of Ms. McGuire's case perfectly. She suffers from some form of CDH and Dr. Alexander specializes in treating other neurologic maladies that afflict adults. Thus, much like Dr. Weig, there appears to be a small, yet noticeable, gap between the doctor's specialty and Ms. McGuire's illness. This gap does not disqualify Dr. Alexander from offering a reliable opinion, but if Ms. McGuire's case required expertise specifically on headaches, then it was not apparent that Dr. Alexander would be of much assistance.

Apart from the slight discordance in background, another flaw in Dr. Alexander's presentation was a series of missteps in his reports. In his reports, Dr. Alexander suggested that various factors other than the HPV vaccine, such as her use of SSRI,[6] oral contraceptives, and analgesics, caused Ms. McGuire's headaches. Exhibit A at 10-12; exhibit C at 8-9. However, in response to information presented during cross-examination, Dr. Alexander modified or retreated from some of his earlier written statements. Tr. 361-91. Thus, Dr. Alexander is encouraged to use more care in how he writes his reports in the future.

Opinion. Dr. Alexander wrote three reports. Exhibits A, C, E. A significant topic was the assertion that Ms. McGuire's headaches were new daily persistent headaches. As noted in footnote 2 above, the dispute over CDH or NDPH turned

[5] UCLA is building a new rehabilitative facility with 138 beds and Dr. Alexander will be the director of that facility when it opens. Tr. 312.

[6] SSRI is defined as "selective serotonin reuptake inhibitor." Dorland's Illustrated Medical Dictionary 1759 (32d ed. 2012).

out to be academic because Ms. McGuire's TNF theory could explain how the HPV vaccine would cause either CDH or NDPH.

Dr. Alexander disagreed with the assertion that the HPV vaccination can cause prolonged headaches of any type and he disagreed with the assertion that the HPV vaccination caused Ms. McGuire's headaches. He noted that the cause of these headaches is unknown.

Dr. Saxon

Background. Dr. Saxon described himself as a "physician-scientist." Tr. 567. He graduated from medical school in 1972. He completed a post-doctorate fellowship in immunology at UCLA in 1977, and became a professor at UCLA. While at the institution, he started the division of immunology within the department of medicine. Tr. 577.

He is board-certified in internal medicine, immunology, and diagnostic laboratory immunology. Tr. 569. His research has focused on immunologic concepts and he has written nearly 200 articles that have appeared in peer-reviewed publications. Tr. 578. In the 1970s, as part of the litigation involving the swine flu vaccine, judges appointed him to advise them. Tr. 582, 678-79.

Dr. Saxon currently spends about 15 percent of his time on medical-legal matters. Tr. 571. Most of his time is spent on biomedical research for companies. Since his retirement from UCLA in 2006, he rarely sees any patients and the patients whom he sees have severe immunologic diseases. Tr. 570.

Dr. Saxon was qualified as an expert in immunology and diagnostic immunology. His testimony demonstrated that among the people who testified, he was the most knowledgeable about immunology and diagnostic immunology. The precision with which he answered questions suggested that he understood and could explain subtle points about immunology. His presentation was thoughtful and engaging.

The one place where Dr. Saxon arguably went awry concerns the disclosure of his opinions. In his testimony, Dr. Saxon described how he investigated the reference levels reported in the Rozen and Swidan article discussed below. Dr. Saxon did not disclose his opinions in a report before trial and he should have given Ms. McGuire's attorney and Dr. Swidan an opportunity to prepare for this testimony. However, Ms. McGuire did not move to strike the testimony during the hearing and neither Ms. McGuire's attorney nor Dr. Swidan requested an opportunity to respond after the hearing. Thus, any procedural deficiencies

associated with a lack of notice are considered waived. Nevertheless, Dr. Saxon is instructed to be mindful about the requirement to disclose opinions in advance of the trial.

Opinion. Dr. Saxon wrote three reports. Exhibits D, F, I. The first report was a general response to Dr. Weig's opinion that the HPV vaccine can cause prolonged headaches. Dr. Saxon asserted that the HPV vaccinations did not contribute to Ms. McGuire's headaches. Dr. Saxon addressed two aspects of Dr. Weig's opinion: the potential role of TNF in headaches as reported in the Rozen and Swidan article and the HPV vaccine's ability to prompt the production of TNF as discussed in the Pinto article. Exhibit D.

Dr. Saxon's next two reports addressed more narrow topics. In exhibit F, he challenged Dr. Swidan's qualifications to opine on immunology. This topic is explored in more detail below. In Dr. Saxon's last report, he responded to Dr. Weig's opinion regarding timing. Exhibit I.

Dr. Swidan

Background. The final expert is Dr. Swidan. Because her background is unusual for an expert who testifies in the Vaccine Program, her education, training, and experience is described in a bit more detail.

After starting her college education at Eastern Michigan University, Dr. Swidan completed four years of study at the University of Michigan, where she received a Doctorate of Pharmacy degree. Exhibit 39 (C.V.) at 1; Tr. 433. A doctorate in pharmacy is not the same as a Ph.D. in pharmaceutical sciences. Tr. 450-52.[7] In obtaining her doctorate in pharmacy, Dr. Swidan studied pharmacology. Tr. 434. Pharmacology is "the science that deals with the origin, nature, chemistry, effects, and uses of drugs; it includes pharmacognosy, pharmacokinetics, pharmacodynamics, pharmacotherapeutics, and toxicology." Dorland's Illustrated Medical Dictionary 1425 (32d ed. 2012); accord Tr. 460-62. Dr. Swidan also learned about immunology, including "antibiotics, antivirals, [and] vaccines." Tr. 435.

[7] The Secretary's cross-examination of Dr. Swidan brought out the distinction between a doctorate of pharmacy and a Ph.D. in pharmacology. Ms. McGuire's counsel's error in characterizing Dr. Swidan's degree appears inadvertent. See Tr. 433-34, 449.

Dr. Swidan's training to earn a doctorate in pharmacy emphasized clinical aspects of pharmacology. (In contrast, people pursuing a Ph.D. in pharmaceutical sciences conduct more research in laboratories.) Tr. 451. Clinical pharmacology, in turn, concerns "help[ing] the physicians make smarter decisions about drug therapy." Tr. 469. Clinical pharmacologists provide this assistance by knowing about the individual patient, confirming that the correct drug was prescribed at the correct dose, and "monitoring for any adverse effects." Id.

After graduating with her doctorate in pharmacy, Dr. Swidan completed a fellowship in biopharmaceutics. Exhibit 39 at 1; Tr. 435. In that position, Dr. Swidan designed clinical trials and wrote reports about the results. Tr. 435-37; exhibit 39 at 11-12 (listing articles).

After Dr. Swidan completed her post-graduate training, she became the clinical coordinator at Chelsea Community Hospital. This hospital is located in a town of about 5,000 people and is affiliated with the larger University of Michigan Health System. Tr. 437-38, 453. Within the Chelsea Community Hospital, an inpatient unit treated people with head and general pain. Dr. Swidan described this as a tertiary care center to which people with refractory headaches from around the world are referred. Tr. 447-48.

Dr. Swidan joined the team who made daily rounds. Tr. 438. When going on rounds, "the physicians taught more disease and diagnosis and neurological type syndromes." Tr. 446. As discussed during cross-examination, Dr. Swidan worked under supervision of a doctor and could not diagnose a patient. Tr. 452, 475. On rounds, Dr. Swidan taught "the pharmacology, treatment of pain syndromes, head pain, some of the reactions, [and] some of the pharmocogenetics." Tr. 446.

Dr. Swidan described "head pain and pain management" as her "clinical interest and love." Tr. 443. Dr. Swidan, as part of a team, has written articles and book chapters about head pain and headache management. Tr. 445, 458; see also exhibit 39 at 11-13. Dr. Swidan's co-authorship of a paper about TNF and chronic headaches led to her retention as an expert witness in this case and there is extensive discussion about that paper in section I.B.3(a), below.

Dr. Swidan stated that she "do[es] 60 to 100 lectures a year in general around the country and internationally in mainly pain management, head pain and neurological conditions," Tr. 444, although her curriculum vitae lists considerably fewer "invited presentations." Her curriculum vitae indicates that she has made

presentations to the Michigan Pharmacists' Association about CDH and to the American Academy of Neurology. Exhibit 39 at 6, 8; see also Tr. 543-44.

In 2007, she stopped working at Chelsea Community Hospital and opened a business called Pharmacy Solutions. She attempts to bring her experience as a clinical pharmacist in a hospital to a larger audience. Tr. 441.

In addition to operating Pharmacy Solutions, Dr. Swidan is also a clinical associate professor of pharmacy at the College of Pharmacy at the University of Michigan. Exhibit 39 at 2. Her teaching focuses on neurology and pain management. Tr. 441-42. In the context of asking Dr. Swidan about her responsibilities as a professor, Ms. McGuire inquired about Dr. Swidan's teaching about pathophysiology. Tr. 442-43.

Dr. Swidan's knowledge about how diseases, particularly headaches, arise is a point of particular controversy. Dr. Swidan explained that as a professor, she teaches pharmacology students "the physiology, how does the body normally work because it's hard to understand what goes wrong if you don't understand how the body normally works." She continued that she reviews "pathophysiology . . . what happens to the body in disease state and then how can we treat the disease." Tr. 443.

When Ms. McGuire attempted to build on this foundation by asking Dr. Swidan to explain how vaccines can cause persistent headaches, the Secretary argued that Dr. Swidan lacked the qualifications to offer an opinion about the cause of headaches. Tr. 474-75. The Secretary maintained that although Dr. Swidan was on a team that treated headache patients, Dr. Swidan did not have the knowledge to comment on the cause of the headaches:

> [Dr. Swidan] always makes her determination with the assistance of a medical doctor with specialized knowledge in the condition. And they inform her of the diagnosis. They inform her of the pathophysiology and then ask her for treatments -- recommendations on treatments.
>
> So, she constantly uses the term "we" and then she assumes the entire knowledge of the team that she is on, despite the fact that she plays a particular role on that team. So, that, I think, is where we're starting to cross over to impute on Dr. Swidan the entire knowledge of the

> teams that she works on, despite the fact that she doesn't have their qualifications or expertise. And that's what I'm trying… to explain there's a difference between the two.

Tr. 477-78.

After the Secretary raised this objection, Dr. Swidan further elaborated upon her training and experience. She stated "it's very important for us [professionals with a doctor of pharmacy degree] to understand the pathophysiology" of diseases such as asthma. Tr. 485. The Secretary did not present any testimony suggesting that clinical pharmacists are not trained in pathophysiology.

In responding to the Secretary's challenge to Dr. Swidan's testimony, Ms. McGuire asserted that Dr. Swidan is qualified to provide opinions because of her "listening to her colleagues, from her education, her training and her background and her specialized knowledge, and it's based on review of the medical literature." Tr. 489-90. In Ms. McGuire view, the Secretary's objection is "not a basis to exclude her testimony, but it's more a question of the weight that [the special master], as a fact finder, assign to that testimony." Tr. 490.

Dr. Swidan was permitted to present her opinions about the causes of headaches and how a vaccination can contribute to the cause of headache. Tr. 491. This evidentiary ruling to admit the opinion was based, in part, on her background in headache pain. See Tr. 471.[8]

The Secretary's argument regarding Dr. Swidan's lack of qualifications raised during the hearing echo an argument presented in a pre-hearing motion. Before the hearing, the Secretary had filed a motion to exclude Dr. Swidan's opinion as unreliable pursuant to Daubert. To support this motion, the Secretary relied, in part, on an opinion from Dr. Saxon that Dr. Swidan "does not have the required scientific expertise to address the issues at hand and failed to employ the

[8] Although Dr. Swidan was admitted as an expert in pharmacology, she was not admitted as an expert in immunology. Dr. Swidan does not have any advanced degree in immunology. Tr. 457. She also could not respond to some questions about immunologic concepts. Tr. 458-59. Dr. Saxon later described this knowledge as "basic" enough that a "first-year graduate student" would have. Tr. 648. The ruling that Ms. McGuire had not shown that Dr. Swidan was qualified in immunology did not prevent Ms. McGuire from asking Dr. Swidan any questions. Dr. Swidan answered every question that Ms. McGuire asked. In other words, no testimony was excluded.

proper scientific approach and methodology in reaching her conclusions." Exhibit F at 1-2. While that motion was pending, the Federal Circuit indicated that a special master should not give less weight to a person with a Ph.D. in immunology than a person who graduated from medical school. Koehn v. Sec'y of Health & Human Servs., 773 F.3d 1239, 1244 (Fed. Cir. 2014). In accord with Koehn, the Secretary's motion to exclude Dr. Swidan's testimony was denied. Order, issued Feb. 19, 2015.

Now, having heard Dr. Swidan's testimony, the undersigned may comment that Dr. Swidan's opinion was not very helpful. Dr. Swidan delivered much less than was promised. Ms. McGuire retained Dr. Swidan to counter the opinion of Dr. Saxon, the immunologist whom the Secretary retained, and to present information about the paper she co-authored with Dr. Rozen. On immunology, the contest between Dr. Swidan and Dr. Saxon was not close. Dr. Saxon possesses expertise in immunology, as reflected in his status as a board-certified internist, clinical immunologist and diagnostic immunologist, that Dr. Swidan lacks. Tr. 569. Dr. Saxon explained relatively sophisticated immunologic concepts in a way that is consistent with someone who has practiced medicine as an immunologist and taught immunology for more than 35 years. In contrast, Dr. Swidan's testimony was often conclusory. The lack of support was particularly glaring when Dr. Swidan attempted to demonstrate that her education (a Ph.D. in pharmacology), and her experience (20 years as a clinical pharmacist) qualified her to opine on the causes of diseases. Although Dr. Swidan and Ms. McGuire's attorney consistently pressed the idea that Dr. Swidan's responsibilities as a clinical pharmacist require her to understand the pathogenesis of diseases, they failed to persuade me, the trier of fact, that Dr. Swidan possesses sufficient knowledge about the causes of relevant diseases that would make her testimony useful.[9]

Dr. Swidan's relative lack of knowledge carried over to the other topic about which she was expected to possess some mastery --- the article about TNF and headaches. Dr. Swidan could not answer many questions about the article that she co-authored, repeatedly saying that Dr. Rozen was responsible for that section. To

[9] Given that the Secretary had filed a motion to exclude Dr. Swidan's testimony before the hearing, it was incumbent on Ms. McGuire's attorney to establish a solid foundation for Dr. Swidan's expertise. Ms. McGuire's attorney's examination into Dr. Swidan's background left many topics unexplained.

some degree, Dr. Saxon's failure to disclose his specific criticisms about the Rozen and Swidan article in advance of the hearing placed Dr. Swidan at a disadvantage. Nevertheless, Dr. Swidan should have been prepared to talk in-depth about the article because (a) the article was one of the two articles most important to Ms. McGuire's case, and (b) Dr. Swidan was retained specifically because she co-wrote that article.

In short, although Dr. Swidan contributed some meaningful information as the citations to her testimony demonstrate, Dr. Swidan fell significantly short in testifying on the topics critical to Ms. McGuire's claim. In the future, an attorney representing a petitioner should consider the strengths and weaknesses in Dr. Swidan's background before retaining her to testify in the Vaccine Program.

Opinion. Dr. Swidan wrote two reports. Exhibit 38 set forth her basic opinion – that the HPV vaccination caused an inflammatory response in Ms. McGuire and this inflammatory response caused her to have headaches. Dr. Swidan emphasized the role of TNF in headaches. In her second report, Dr. Swidan, after reviewing Dr. Saxon's criticism of both her background and her opinion, confirmed her opinion that the HPV vaccination caused Ms. McGuire's headache. Exhibit 41.

Ms. McGuire's Medical Background

The October 12, 2012 Revised Findings of Fact resolved one critical aspect of this case: when Ms. McGuire's headaches began. During most of the litigation, the details about Ms. McGuire's headaches seemed important because Dr. Weig stated that she suffered from NDPH and Dr. Alexander, in contrast, opined that she suffered from CDH. Exhibit 28 (Dr. Weig); exhibit A (Dr. Alexander). However, this dispute about diagnosis turned out to be insignificant because Ms. McGuire's experts presented a theory through which the HPV vaccine can cause either NDPH or CDH. See Resp't's Status Rep., filed Mar. 11, 2015. Eliminating the arguments about diagnosis simplifies Ms. McGuire's case. Many of the details about the quality, duration, location, and intensity of her headaches are not material. Consequently, this decision discusses Ms. McGuire's medical records relatively summarily, although the medical records themselves have been reviewed thoroughly.

Health before Vaccination

Ms. McGuire was born in 1987. Exhibit 2 at 1. Her father suffered from cluster headaches at least once. Exhibit 4 at 1; Tr. 85, 99. Dr. Alexander asserted

that Ms. McGuire's genetic background may have contributed to her headaches. Tr. 325.

In 2003, Ms. McGuire sought treatment for a panic disorder. She was prescribed Zoloft. Exhibit 22 at 130-31, 126; see also Tr. 34-35. Ms. McGuire continued to take Zoloft until the summer 2004. But, after she stopped taking Zoloft, her anxiety returned and she resumed the prescription. Exhibit 22 at 118-22.

In August 2006, Ms. McGuire saw Robert M. Levenson, her pediatrician. Ms. McGuire reported that she had returned from a cruise to Bermuda slightly more than two weeks earlier. After coming home, Ms. McGuire had a sudden onset of frontal headaches, tiredness, malaise and an achy neck and shoulders for two weeks. Dr. Levenson prescribed Fioricet and recommended therapeutic massages. Exhibit 1 at 107-08; see also Tr. 30-31, 54 (Ms. McGuire's testimony that a medical record ostensibly referring to a headache in December 2006 was actually referring to her August 2006 headache); cf. Tr. 328-29, 370-71, 472.

Approximately one year later in August 2007, Ms. McGuire went to an urgent care center for anxiety and panic attacks. She also reported symptoms of depression after stopping Zoloft in January that year. The doctor prescribed lorazepam. Exhibit 1 at 93-94.

In September 2007, Ms. McGuire was working as a medical assistant for Harvard Vanguard Medical Associates. Exhibit 21 (employment records) at 1; see also Tr. 9, 103 (describing duties). She was also attending nursing school in the evening. Exhibit 20 (school records). She described herself as "healthy and active." Exhibit 17 (affidavit) at 1; accord Tr. 9-10.

On September 20, 2007, Ms. McGuire saw Laura Tremblay, her primary care physician, for a complete physical examination. Ms. McGuire said that she was having various gastrointestinal and gynecological complaints, but after Dr. Tremblay's review, she said all other systems were negative. At this appointment, Ms. McGuire received the first dose of the HPV vaccine. Exhibit 1 at 88-89; see also Tr. 36.[10]

[10] Ms. McGuire averred that after receiving the vaccination, she left work because she felt ill. Specifically, she had a fever and headache, was nauseated, and vomited. Exhibit 17 at 1; Tr.

(continued…)

Health after Vaccination

Between October 25 and October 28, 2007, Ms. McGuire began having headaches that were initially intermittent. One week after the headaches began, Ms. McGuire's headaches became constant. Revised Findings, issued Oct. 12, 2012. Ms. McGuire took over-the-counter medications, which did not help. Nonetheless, she continued to work and to attend school. Tr. 11-12.

On November 14, 2007, Ms. McGuire received the second dose of the HPV vaccine. Exhibit 1 at 86. Approximately four months later, Ms. McGuire told her neurologist that there "was no change in her headache after the second vaccine." Id. at 54; see also Tr. 73; cf. Tr. 222.[11] On November 20, 2007, Ms. McGuire had a nutrition assessment. Exhibit 1 at 86; Tr. 47.[12]

Ms. McGuire recalled that after having a headache for many weeks, she became concerned that her headache had not stopped. In addition, the severity was increasing. Tr. 14-15, 52. Therefore, on December 9, 2007, she went to seek assistance at an urgent care facility associated with her employer, Harvard Vanguard Medical Associates. Tr. 15. She stated that she had been having headaches for six weeks before her appointment. Exhibit 1 at 83-84; see also Tr. 47-48. In terms of a more recent history, Ms. McGuire's report appears to be

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11, 37-39, 119. She made similar statements to doctors treating her months later. See exhibit 1 at 54 (Mar. 20, 2008); exhibit 3 at 77 (Apr. 23, 2008).

Ms. McGuire's experts did not mention her illness on September 20, 2007. Exhibit 28 (Dr. Weig's rep.) at 1; exhibit 38 (Dr. Swidan's rep.) at 3. However, Dr. Swidan did briefly testify that Ms. McGuire "was sick with a febrile illness" and that the blood-brain barrier can be leaky in sick patients. Tr. 526.

[11] Ms. McGuire testified that about a week and a half after the second dose of HPV vaccination, her headaches changed from intermittent to constant. Tr. 13, 43-44, 91-92, 123-24. However, her recollection is not consistent with several medical records that do not mention a change in her headache quality or frequency after the second dose of the HPV vaccine. See exhibit 1 at 46 (record dated May 17, 2008), 54 (record from March 20, 2008); exhibit 3 at 73-76 (record dated June 17, 2008); see also Tr. 222-24, 340-43; but see exhibit 11 at 12 (record dated Aug. 31, 2009); Tr. 299.

[12] Ms. McGuire did not discuss her headaches with the dietician. In Dr. Alexander's opinion, this omission is inconsistent with a claim that she was suffering from severe headaches. Tr. 335-36, 402. In contrast, Dr. Weig did not perceive any inconsistency because people would not normally talk to a dietician about their headaches. Tr. 423.

inconsistent. At one place, Ms. McGuire said that, "for the past two weeks" (that is, starting around Thanksgiving), she was feeling frontal pressure. Exhibit 1 at 83; see also Tr. 51-52; cf. exhibit 3 at 3 (a Dec. 23, 2007 emergency department record suggesting frontal headaches started four weeks earlier); Tr. 60-61 (Ms. McGuire's testimony about the Dec. 23, 2007 record); Tr. 215. Yet, later within the same paragraph, Ms. McGuire stated that "Symptoms have not accelerated, and there was no change in location or quality in the past 2 weeks." Exhibit 1 at 83; see also Tr. 219, 337.

While hospitalized, Ms. McGuire underwent many tests, including a lumbar puncture and MRIs. Exhibit 1 at 72-74. After the lumbar puncture, her headaches worsened. Id. at 73; see also Tr. 218-19 (Dr. Weig), 340 (Dr. Alexander).

For the remainder of December 2007 and continuing into January 2008, Ms. McGuire saw many doctors for her headaches and those doctors prescribed a variety of pharmaceuticals. The attempted interventions did not provide any lasting relief. See exhibit 1 at 63-81; exhibit 3 at 17-18 (admission to the emergency room), 80-81 (discharge); Tr. 16-21, 53-68.[13]

Throughout 2008, Ms. McGuire visited several more doctors but they did not help alleviate her symptoms. Some of these histories indicate that Ms. McGuire's first HPV vaccination preceded the onset of her headaches in October 2007. However, none of these doctors stated that the vaccination caused her headaches. See exhibit 1 at 54-55; exhibit 3 at 78-79; exhibit 5 at 2; exhibit 1 at 46-47, 36-37; exhibit 3 at 32-34; exhibit 9 at 8; exhibit 3 at 66-67; see also Pet'r's Preh'g Br. at 34-36 (quoting medical records).

During a hospitalization in 2008, a doctor prescribed a short course of prednisone. Exhibit 1 at 41, 46-47; see also Tr. 196, 355, 474. Prednisone is a "synthetic glucocorticoid… [used] as an antiinflammatory and immunosuppressant in a wide variety of disorders." Dorland's at 1508. Ms. McGuire later informed her doctors that the course of prednisone did not help her headaches and may have made them worse. Exhibit 3 at 70 (Dr. Klein's letter, dated July 30, 2008); exhibit

[13] Ms. McGuire's (over)use of medication likely contributed to the continuation of her headaches. Tr. 206, 269, 322-25, 393. Because Ms. McGuire started taking medication after her headaches became chronic, the Secretary has not argued that Ms. McGuire's use of medication caused her headaches. Tr. 394.

12 at 3 (report, dated Dec. 10, 2008); exhibit 13 at 1 (Dr. Herzog's letter, dated Aug. 16, 2010).

On January 15, 2009, Ms. McGuire went to the Osher Clinical Center for Complementary and Integrated Medical Therapies, where she saw Donald Levy, M.D. Dr. Levy stated that because Ms. McGuire "never had headaches before the HPV vaccination," there was a causal connection between the vaccination and the headache. Exhibit 12 at 9; see also Tr. 191-92, 268, 411-13.

In the remainder of 2009, Ms. McGuire saw doctors less frequently. Exhibit 2 at 2; exhibit 8 at 4; exhibit 11 at 3, 12-13; exhibit 16 at 13-15.

On July 13, 2010, Ms. McGuire saw Andrew Herzog, M.D. at the Neuroendocrine Associates at Harvard Medical School. She stated that her headaches started "within 2 hours of the [HPV vaccine] injection." Exhibit 13 at 12. She also said that before the vaccination, she had never had headaches. Dr. Herzog stated that although headaches have been reported to follow HPV vaccinations, a long-lasting headache would be unusual. He suggested an evaluation for an immune-mediated process. Id. at 13; see also Tr. 190. However, this investigation did not reveal any abnormalities that would cause headaches. Exhibit 13 at 5-11; see also Tr. 266, 412-13.

Despite the continuing problems with headaches, Ms. McGuire graduated from nursing school in December 2010. She passed her examinations in March 2011, and became a registered nurse. Exhibit 35 (Ms. McGuire's affidavit, describing her employment history) at 1; Tr. 22. She worked as a registered nurse for approximately two years, but then her headaches prevented her from working. Exhibit 35 at 2; see also Tr. 23, 107.

Standards for Adjudication

A petitioner is required to establish her case by a preponderance of the evidence. 42 U.S.C. § 300aa–13(1)(a). The preponderance of the evidence standard requires a "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010) (citations omitted). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991).

Distinguishing between "preponderant evidence" and "medical certainty" is important because a special master should not impose an evidentiary burden that is

too high. Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1379-80 (Fed. Cir. 2009) (reversing special master's decision that petitioners were not entitled to compensation); see also Lampe v. Sec'y of Health & Human Servs., 219 F.3d 1357 (Fed. Cir. 2000); Hodges v. Sec'y of Health & Human Servs., 9 F.3d 958, 961 (Fed. Cir. 1993) (disagreeing with dissenting judge's contention that the special master confused preponderance of the evidence with medical certainty).

The elements of Ms. McGuire's case are set forth in the often cited passage from the Federal Circuit's decision in Althen: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005).

Analysis

The three prongs of the Althen test are evaluated in separate sections below. The order of presentation begins with theory, which outlines petitioner's proposed theory and the relevant evidence and case law. The next issue is the timing and the last factor is the "logical sequence of cause and effect." Each section analyzes the evidence (medical records, testimony and medical literature) in relation to the relevant precedent.

I. Theory

The first Althen prong requires "a medical theory causally connecting the vaccination and the injury." 418 F.3d at1278. Because Ms. McGuire's injury is chronic headaches, basic information about headaches is provided as a foundation. Against this backdrop, Ms. McGuire bears the burden of presenting a theory to explain how the HPV vaccine can cause chronic headaches. Veryzer v. Sec'y of Health & Human Servs., 100 Fed. Cl. 344, 355 (2011), aff'd per curiam, 475 F. App'x 765 (Fed. Cir. 2012).

Ms. McGuire attempted to meet her burden in two ways. As explained in section B below, Ms. McGuire presented evidence – testimony from Dr. Weig and Dr. Swidan. In addition, as explained in section C below, Ms. McGuire presented an argument based on a recent case from the Federal Circuit.

A. Overview of Primary Headaches

Medical science does not know the cause of primary headaches.[14] See exhibit 38, tab U (Rozen and Swidan) at 1053 (stating the "pathogenesis of NDPH is unknown"), exhibit 40, tab C (Sanjay Prakash & Nilima Shah, Post-infectious New Daily Persistent Headache May Respond to Intravenous Methylprednisolone, J. Headache Pain 2010; 11:59-66) at 59 (stating that for NDPH, the "pathophysiology is largely unknown"), Tr. 317.

However, there are some generally accepted beliefs about the pathogenesis of primary headaches. A vastly simplified summary is that a headache begins with some irritant to the trigeminal nerve.[15] Once the trigeminal nerve is disturbed, the body produces various substances, including calcitonin gene-related peptide (CGRP), that perpetuate a cycle. Tr. 317-18, 476, 491-93.

Many aspects about the etiology of chronic headaches are undetermined. For example, scientists have not identified the initial trigger (or triggers). Scientists have recognized that infections, surgery, and stressful life events sometimes precede the onset of chronic headaches. Exhibit 38, tab U (Rozen and Swidan) at 1053; exhibit 40, tab C (Prakash) at 59 (abstract). However, these preceding factors have not been determined to be causes of the headaches. Tr. 682-83 (Saxon).

In addition to the uncertainty about the cause of headaches, there are questions about why a headache is prolonged. Commonly, headaches resolve after a few hours and/or after medications. The headaches that Ms. McGuire suffers differ in that they are chronic and refractory to treatment. The factor or factors contributing to the headache's chronicity and resistance to treatment are undetermined. Tr. 495-96.

A current theory is that CGRP is part of a cycle with the cytokine TNF. Cytokines are proteins that a cell releases to communicate with another cell during

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[14] Primary headaches are not the same as secondary headaches. Secondary headaches are headaches associated with another disorder, such as meningitis. Tr. 153, 316, 602-03.

[15] The trigeminal nerve, which is also known as the fifth cranial nerve, is a sensory nerve for the face, teeth, mouth, and nasal cavity. It is also the motor nerve for chewing. Dorland's at 1260; see also Dorland's at 1246 (illustration).

the generation of an immune response. Dorland's at 466; see also Tr. 179, 350, 606. Although Dr. Weig characterized TNF as a proinflammatory cytokine, Tr. 179, Dr. Saxon disagreed. Dr. Saxon asserted that TNF is used in more than 100 biologic activities. Tr. 606. Dr. Saxon supported his view that TNF is not always a proinflammatory cytokine by pointing to the Pinto article, which is discussed in more detail below. Tr. 631-35, citing exhibit D, tab 16 (Ligia Pinto et al., HPV-16 L1 VLP Vaccine Elicits a Broad-Spectrum of Cytokine Responses in Whole Blood, 23 Vaccine 3555 (2005)).[16]

B. Evidence relating to HPV Vaccines Causing Headaches

Ms. McGuire presented testimony from Dr. Weig and Dr. Swidan that the HPV vaccine can cause headaches. Tr. 177, 509-11. The theory Ms. McGuire proposes seems to contain at least three distinct steps. First, the HPV vaccine promotes the production of various cytokines, including TNF. Second, from the body's periphery, TNF crosses the blood brain barrier to reach the central nervous system. Third, in the central nervous system, TNF causes inflammation producing headaches. See Pet'r's Preh'g Br. at 17-18.

1. Does the HPV Vaccine Promote the Production of TNF?

The first step in the petitioner's theory is the administration of the HPV vaccine increases the level of TNF. For this proposition, Dr. Weig and Dr. Swidan rely upon the Pinto article. Exhibit 28 (Dr. Weig) at 4; Tr. 179, 253 (Dr. Weig), 516 (Dr. Swidan).

In the Pinto experiment, blood from women was drawn and tested to set baseline measuring points. Then, some women received a dose of a vaccine against some strains of the human papillomavirus (but not the same vaccine as Ms. McGuire received) and some women received a placebo. The participants received another dose or placebo one month later; one month after the second dose, the researchers drew a second sample of the women's blood. The women received a third dose of the vaccine (or placebo) and after waiting another month, the researchers drew a third sample. Exhibit D, tab 16 (Pinto) at 3556.

[16] In addition to the literature, another reason for crediting Dr. Saxon over Dr. Weig is that Dr. Saxon specializes in immunology. Dr. Weig stated that he would defer to an immunologist. Tr. 279.

The blood samples were cultured in vitro for 24 hours and then the amount of cytokines was measured. The testing showed that the women who received the vaccine produced higher amounts of TNF than the women who did not. Tr. 632-41 (Dr. Saxon). This result is not surprising because the vaccine is designed to prompt a response from the immune system. Tr. 511 (Dr. Swidan). Thus, the Pinto experiment supports one aspect of the petitioner's theory: HPV vaccine elevates the amount of TNF.

However, there are two problems with how Ms. McGuire seeks to employ the Pinto article. The first, and less significant, issue is that the Pinto experiment was conducted in vitro, not in vivo. Tr. 258, 643. An extrapolation from a petri dish to human beings may be reasonable, but there needs to be some basis for the extrapolation. "As a general matter, it may be that in vitro tests are not reliably predictive of human safety." Bristol-Meyers Squib Co. v. Teva Pharma. USA, Inc., 769 F.3d 1339, 1355 n.5 (Fed. Cir. 2014) (Taranto, J.) (dissenting from denial of reh'g en banc) (citing Reference Manual on Scientific Evidence). In other cases, special masters have commented on the problems with using in vitro studies. See Kolakowski v. Sec'y of Health & Human Servs., No. 99-625V, 2010 WL 5672753, at *85-86 (Fed. Cl. Spec. Mstr. Nov. 23, 2010); Dwyer v. Sec'y of Health & Human Servs., No. 03-1202V, 2010 WL 892250, at *131-32 (Fed. Cl. Spec. Mstr. Mar. 12, 2010). Ms. McGuire did not provide a reliable reason for making a jump of this kind.

The second and more significant issue concerns the amount of TNF produced in the Pinto experiment. As Dr. Saxon pointed out, the Pinto authors did not conclude that the amount of cytokine produced was pathologic. Tr. 643-44. Some evidence regarding the amount of TNF produced as part of a normal reaction to a vaccine compared to an adverse reaction to a vaccine would have been helpful because Dr. Weig's theory asserts that the HPV vaccine caused an "excessive" amount of TNF. Tr. 281. This assertion is particularly unsupported because Dr. Weig admitted that he did not know the amount of TNF that was required to cause a disease. Tr. 247.

While the lack of support for Dr. Weig's opinion is problematic for Ms. McGuire, the Secretary introduced evidence contradicting the assertion that the amount of cytokines produced was pathologic. This evidence was the most recent report on vaccines and adverse reactions from the Institute of Medicine ("IOM"). Exhibit D, tab 4 (Kathleen Stratton et al., Adverse Effects of Vaccines: Evidence and Causality, Institute of Medicine (2012)). Due to the credentials and expertise of the members of the Institute of Medicine, special masters have consistently placed great weight on their reports and appellate courts have consistently found

the crediting of these reports not arbitrary. See Porter v. Sec'y of Health & Human Servs., 663 F.3d 1242, 1252–54 (Fed. Cir. 1993) (2002 report); Cucuras v. Sec'y of Health & Human Servs., 993 F.2d 1525, 1529 (Fed. Cir. 1993) (1991 report); Isaac v. Sec'y of Health & Human Servs., 108 Fed. Cl. 743, 768–74 (2013), aff'd, 540 F. App'x 999 (Fed. Cir. 2013) (2011 pre-publication report); Terran v. Sec'y of Health & Human Servs., 41 Fed. Cl. 330, 337 (1998) (1991 report and different 1994 report), aff'd, 195 F.3d 1302, 1317 (Fed. Cir. 1999); Kelley v. Sec'y of Health & Human Servs., 68 Fed. Cl. 84, 91 n.11 (2005) (1994 report); Kuperus v. Sec'y of Health & Human Servs., No. 01–60V, 2003 WL 22912885, at *10 (Fed. Cl. Spec. Mstr. Oct. 23, 2003) (1994 report). In its most recent report, the IOM found "no evidence that directly or indirectly supports the oversecretion of cytokines as an operative mechanism." Exhibit D, tab 4 (Stratton) at 76 [pdf 3]. Ms. McGuire introduced no persuasive evidence to rebut the IOM's conclusion that no evidence supports a conclusion that cytokines cause a disease.

2. Does TNF Cross the Blood Brain Barrier?

Because the HPV vaccine is given intramuscularly (exhibit 19 at 2), the initial reaction whereby the cytokine TNF is recruited occurs near the site of injection. Exhibit 38 (Dr. Swidan's report) at 9. To reach the brain, the TNF must enter the bloodstream and cross the blood brain barrier. The blood brain barrier separates the vital parts of the central nervous system from the blood and contains anatomical and physiological components. Dorland's at 201. The mechanism by which TNF penetrates the blood brain barrier is unclear. Exhibit 28 (Dr. Weig's report) at 4.

The Secretary's cross-examination of Dr. Swidan revealed that the crossing of the blood brain barrier was a second step in her theory. Tr. 525-26. However, how TNF would cross the blood brain barrier was not explained very well. Dr. Weig admitted that TNF would not easily cross the blood brain barrier. Tr. 181.

Dr. Swidan proposed that a rise in TNF in the body's periphery could cause the blood brain barrier to become leaky. Tr. 562. She further asserted that the fever Ms. McGuire experienced within two days of the vaccination was evidence of a systemic reaction. Tr. 526.

However, the medical doctors did not agree with Dr. Swidan. Dr. Weig, as noted above, asserted that the TNF does not easily cross the blood brain barrier. Even after hearing Dr. Swidan's testimony, Dr. Weig acknowledged that he did not know whether TNF creates permeability in the blood brain barrier. Tr. 709.

Likewise, Dr. Saxon stated that he had never heard of a leaky blood brain barrier. Tr. 692-93.

Whether cytokines can cross the blood brain barrier appears to be a topic on which medical doctors, especially a neurologist like Dr. Weig, would have more training and experience than a pharmacologist. Dr. Swidan presented no support for her assertion that TNF can cross the blood brain barrier. Thus, her opinion on this point lacks reliability, undermining Ms. McGuire's proof on prong one.

3. Does TNF Contribute to Headaches?

The final step in Ms. McGuire's theory concerns what happens after TNF crosses the blood brain barrier and enters the central nervous system. On this point, Dr. Weig's and Dr. Swidan's opinions were unclear. At times, they seemed to suggest that TNF caused the headache. Exhibit 28 at 4 (Dr. Weig's Rep.) (TNF increases production of peptide (CGRP) implicated in migraine pathogenesis); exhibit 30 at 5 (Dr. Weig's Supp'l Rep.) ("Elevated TNF alpha appears to be a causative agent for multiple forms of headache."); exhibit 38 at 12 (Dr. Swidan's Rep.) (TNF induces CGRP, a known factor in migraine pathogenesis); Tr. 516-17 (Dr. Swidan). At other times, they seemed to suggest that TNF only made a headache worse (either in duration or severity). Tr. 704-05 (Dr. Swidan) (TNF "amplifies" CGRP production; Tr. 202-04 (Dr. Weig) (headaches "substantially… worsened" after second HPV vaccine); see also Tr. 614-17 (Dr. Saxon).

Ms. McGuire's pre-trial brief identified an article whose authors are Dr. Rozen and Dr. Swidan as the primary basis for the theory that TNF contributes to headaches. Pet'r's Preh'g Br. at 26 (stating "the two articles of utmost importance to [Ms. McGuire's] theory [are] the Pinto article… and the Rozen and Swidan article"). However, for the reasons explained below, Ms. McGuire's reliance on the Rozen and Swidan article is misplaced. Nevertheless, this problem is not fatal to Ms. McGuire's case because other evidence, including a study by Dr. Durham and the testimony of Dr. Saxon, support a finding that TNF contributes to headaches.

a) Rozen and Swidan

Background. Dr. Rozen and Dr. Swidan designed a study to determine whether their patients with refractory headaches were experiencing inflammation. After Dr. Rozen diagnosed the patients, he ordered a spinal tap. Dr. Rozen sent the cerebrospinal fluid and a blood sample to a laboratory, ARUP Laboratories, for

testing. Dr. Rozen and Dr. Swidan were looking for evidence of pro-inflammatory cytokines. Tr. 495-500, 527-30.

ARUP Laboratories determined the reference range for the presence of cytokines in the blood and the reference range for the presence of cytokines in the cerebrospinal fluid by testing 36 volunteers. For both substances, the reference range was less than 8.2 picograms per milliliter (pg/mL). In the published article, Dr. Rozen stated that ARUP Laboratories disclosed the reference ranges via a "personal communication." Exhibit 38, tab U (Todd Rozen and Sahar Swidan, Elevation of CSF Tumor Necrosis Factor α Levels in New Daily Persistent Headache and Treatment Refractory Chronic Migraine, 47 Headache 1050 (2007)) at 1051. Dr. Swidan testified that ARUP Laboratories provided the information about reference ranges to Dr. Rozen only, not to her. Tr. 531-32.

Dr. Rozen and Dr. Swidan compared the amount of TNF in their 38 patients with refractory headaches with the amount of TNF in 36 normal individuals as determined by ARUP Laboratories. The amount of TNF in the serum was similar in both groups. However, the cerebrospinal fluid from patients with refractory headaches contained more TNF than the cerebrospinal fluid from volunteers at ARUP Laboratories. Exhibit 38, tab U at 1051-52. Dr. Rozen and Dr. Swidan wrote: "TNF [alpha] levels are elevated in various forms of [CDH]." Id. at 1053.

From this observation, Dr. Rozen and Dr. Swidan hypothesized that "[p]ersistent elevation of TNF [alpha] could lead to persistent elevation of CGRP, and thus daily head pain." Id. Similarly, they asserted that "an increase in TNF [alpha] levels in the CSF may play a true role in the pathogenesis of CDH." Id. at 1054. If so, pharmaceuticals that inhibit the production of TNF [alpha] could have "an important role in the treatment of NDPH and refractory chronic migraine." Id. at 1055. However, Dr. Rozen and Dr. Swidan cautioned that their work "is an initial observation, which must be substantiated by future studies." Id. at 1054.

Both Dr. Weig and Dr. Swidan relied upon the Rozen and Swidan study. See exhibit 28 (Dr. Weig) at 3-4; exhibit 38 (Dr. Swidan) at 11.

Criticisms. Through Dr. Saxon, the Secretary raised several arguments against the usefulness of the Rozen and Swidan article.

First, Dr. Saxon challenged the way ARUP Laboratories determined the reference range for TNF in cerebrospinal fluid --- testing 36 healthy volunteers.[17] A reference range is a set of values in which 95 percent of people fall. Tr. 624; see also Dorland's at 2021 (defining reference values). Dr. Saxon argued that a reference range for a laboratory test should involve at least a few hundred participants. Tr. 625-26. Dr. Saxon's opinion was based upon his qualification as a board-certified expert in internal medicine, clinical immunology and diagnostic immunology. His opinion was not challenged at all.

Second, Dr. Saxon questioned the values in ARUP Laboratories' reference ranges for TNF in the serum and in the cerebrospinal fluid. Dr. Saxon indicated that having the same reference range (< 8.2 pg/ML) is "most unusual." Tr. 609-10. In his experience, Dr. Saxon has never before encountered a pair of tests in which the normal levels were the same in the blood and cerebrospinal fluid. Tr. 625.[18] Dr. Swidan's experience was similar. When asked whether she was aware of any test in which the reference range was the same for CSF and serum, Dr. Swidan answered: "I don't know if I can answer that with my knowledge because that's a pathologist's training. . . . And, so, there may be, but I do not know of any." Tr. 535.

A third question of the ARUP Laboratories' reference ranges concerned the current reference ranges. Dr. Saxon stated that shortly before trial, he called ARUP Laboratories to ask about the reference range for TNF. Tr. 688-89. ARUP Laboratories told him that the reference range for TNF from the serum was less than 22 pg/ML. Tr. 610, 625. Assuming that normal TNF levels are the same in blood as they are in cerebrospinal fluid, then an expected CSF level would be 22 pg/ML. If this is also correct, then Dr. Rozen and Dr. Swidan did not discover anything significant because the TNF level in all the patients was less than 22 pg/ML. In other words, the patients would fall within the reference range. Tr. 538, 627-28.

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[17] While healthy people may provide blood samples for testing routinely, healthy people do not undergo spinal taps usually. See Tr. 550 (Dr. Swidan: "we can't just spinal tap people without valid reason"), 630 (Dr. Saxon wondering whether an internal review board would approve a study subjecting healthy people to spinal taps).

[18] Dr. Saxon's background in diagnostic immunology gives him expertise in determining whether tests have clinical value. Tr. 586-87.

Assessment. Overall, these criticisms diminish the reliability of the Rozen and Swidan article.[19] Before the hearing, Dr. Swidan's authorship of this paper was a stated basis for Ms. McGuire's decision to retain her to testify about the immunologic etiologies for chronic headaches. See Pet'r's Preh'g Br. at 25 ("Dr. Swidan's testimony is offered as that of an expert in . . . specifically, the aforementioned medical article she co-authored"). However, it is now evident that Dr. Swidan's role in conducting the experiments and preparing the results for publication was limited. She did not communicate with ARUP Laboratories. Tr. 531-32. Therefore, she could not defend (or even explain) the lab's reference ranges. Her reliance on the work of Dr. Rozen underscored her relative lack of experience.

Apart from these concerns about the foundations for the Rozen and Swidan paper, there are additional problems. Dr. Rozen and Dr. Swidan recommended that future studies substantiate their findings. Exhibit 38, tab U (Rozen & Swidan) at 1054. However, neither Dr. Saxon nor Dr. Swidan was aware of any work that also found elevations in TNF in patients' CSF.[20] Tr. 350-52, 699 (Dr. Saxon); Tr. 546 (Dr. Swidan). Thus, substantiation remains lacking.

Consistent with the lack of confirmation for the novel finding in the Rozen and Swidan paper, the authors' recommendation that doctors prescribe TNF inhibitors to patients suffering from chronic headaches has not been followed. Dr. Weig (Ms. McGuire's expert) does not prescribe TNF inhibitors to his patients

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[19] Although Dr. Saxon had prepared reports addressing the Rozen and Swidan article (see exhibit F at 8), he had not disclosed any criticism of the reference ranges from the ARUP Laboratories. See exhibits D, F, I.

At hearing, when an expert attempts to present an opinion not disclosed before hearing, the opposing party may seek to strike that testimony. E.g. Childers v. United States, 116 Fed. Cl. 486, 596-99 (2013) (granting motion to strike testimony). However, Ms. McGuire's attorney did not attempt to strike Dr. Saxon's opinion during the hearing when any perceived prejudice could have been mitigated. Consequently, Ms. McGuire's failure to move to strike the testimony constitutes a waiver of the argument that the Secretary had failed to disclose Dr. Saxon's opinions in advance of the hearing. See Vaccine Rule 8(f).

[20] Dr. Saxon recognized that other articles published in peer-reviewed journals have cited the Rozen and Swidan article. Tr. 698. While these sources have cited the Rozen and Swidan article, these investigators have not independently verified that people who suffer from chronic headaches have elevated TNF in the cerebrospinal fluid. Id.; Tr. 628.

with chronic headaches. Tr. 264. Dr. Alexander similarly does not prescribe TNF inhibitors. Tr. 414.

Collectively, these factors undermine the value of the Rozen and Swidan article. Although Ms. McGuire characterized this article as "peer-reviewed, published, and well-accepted," Pet'r's Preh'g Br. at 26, Ms. McGuire did not present any persuasive evidence that the article is "well-accepted."[21] In another place, Ms. McGuire described the Rozen and Swidan article as "[r]eliable." Id. at 17. But, Dr. Saxon's testimony with respect to the reference ranges has called into question the reliability of the findings in the Rozen and Swidan article. Dr. Swidan could not answer these challenges.

b) Other Evidence

Although Ms. McGuire's pre-hearing brief emphasized the Rozen and Swidan article, this article provides very little, if any, support for the claim that TNF contributes to headaches. The evidence that more persuasively assists Ms. McGuire in connecting TNF and headaches comes from one of the Secretary's experts, Dr. Saxon.

Based primarily on experiments reported by Dr. Paul Durham (exhibit 28, tab G (Paul Durham, Calcitonin gene-related peptide (CGRP) and migraine, 46 Headache S3 (2006))), Dr. Saxon testified that TNF is part of an amplification process. He stated that the irritation of the trigeminal nerve and associated production of CGRP is the equivalent of placing a car key in the ignition and turning it. Tr. 614. Both start a process. Dr. Saxon continued the analogy by saying that increasing TNF is like stepping on the gas pedal. Tr. 614, 702-03.[22]

This testimony from Dr. Saxon is sufficient to find that Ms. McGuire has established the third step in her three-part theory. It is more-probable-than-not that

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[21] Ms. McGuire's submission of the article from the journal Headache established that it was "published." Although Ms. McGuire did not present any evidence that Headache subjects articles to a peer-review process, the undersigned assumes that there was a peer-review process.

[22] Dr. Weig asserted that the Perini article complements the Durham article. Tr. 183, citing exhibit 38, tab Q (Francesco Perini et al., Plasma Cytokine levels in Migraineurs and Controls, 45 Headache 926 (2005)). Although Dr. Saxon raised some questions about methods of specimen collection and statistical analysis of the Perini article (Tr. 617-20), Perini still supports an argument that elevations in TNF contribute to chronic headaches.

the addition of exogenously produced TNF would cause a person to suffer headaches that are more severe or more prolonged than otherwise.[23]

However, Ms. McGuire's evidence on the first two steps of her three-part theory falls short of being persuasive. In particular, the following questions undermine the persuasiveness of the theory causally connecting the HPV vaccine and chronic headaches:

- Is the amount of TNF produced after vaccination an amount sufficient to cause a disease?
- Is there a reliable basis for extrapolating the Pinto experiment from in vitro to in vivo?
- Is there a reliable basis for finding that TNF crosses the blood brain barrier?

On these points, Ms. McGuire has produced a measure of evidence, consisting of the testimony of Dr. Weig and Dr. Swidan, but did not shore up their opinions by referring to any literature. As an abstract legal principle, petitioners may establish that they are entitled to compensation without presenting any medical literature. Althen, 418 F.3d at 1274. "However, it should be obvious to petitioner that a scientific theory that lacks any empirical support will have limited persuasive force." Caves v. Sec'y of Health & Human Servs., 100 Fed. Cl. 119, 134 (2011), aff'd per curiam, 463 F. App'x 932 (Fed. Cir. 2012). Special masters are not required to accept the opinion of any expert, particularly one who expresses opinions without support. Cedillo v. Sec'y of Health & Human Servs., 617 F.3d 1328, 1347-48 (Fed. Cir. 2010).

C. Argument based upon Precedent

Despite the evidentiary shortcomings in her presentation, Ms. McGuire draws support from the Federal Circuit's opinion in Koehn. Ms. McGuire states

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[23] The finding that the evidence supports Ms. McGuire's assertions on the third step fully makes up for any prejudice that she may have suffered with respect to the undisclosed criticisms of the Rozen and Swidan article. Any mistakes of Ms. McGuire's attorney in not objecting to Dr. Saxon's criticisms as undisclosed or in failing to request rebuttal testimony from Dr. Swidan did not harm Ms. McGuire. Ms. McGuire achieved the result she wanted – a finding that TNF can worsen headaches – by a different path without relying solely on the Rozen and Swidan article.

that in Koehn the Federal Circuit upheld a theory that is "profoundly similar" to her own. Ms. McGuire appears to be implying that the similarities between her case and Koehn support a similar outcome in her case. Pet'r's Preh'g Br. at 20. To assess the comparability of the cases, the facts of Koehn are set forth.

In Koehn, the petitioner's expert presented a two-step theory. The first proposition was that inflammatory cytokines can cause systemic juvenile idiopathic arthritis and the second proposition was that the HPV vaccine prompts the induction of inflammatory cytokines. Koehn v. Sec'y of Health & Human Servs., No. 11-355V, 2013 WL 3214877, at *21 (Fed. Cl. Spec. Mstr. May 30, 2013), mot. for rev. denied, 113 Fed. Cl. 757 (2013), aff'd, 773 F.3d 1239 (Fed. Cir. 2014).

Pursuant to Terran v. Sec'y of Health & Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999), the undersigned special master evaluated this theory according to the factors that the Supreme Court articulated in Daubert v. Merrell Dow Pharma., Inc., 509 U.S. 579 (1993), and found that the theory was not persuasive. Koehn, 2013 WL 3214877, at *22-26. Separately, the undersigned also found that the petitioner did not establish the third prong of Althen, which concerns timing. Id. at *26-29. The Court of Federal Claims denied a motion for review, finding that the special master's findings for both Althen prong 1 and Althen prong 3 were not arbitrary. C.K. v. Sec'y of Health & Human Servs., 113 Fed. Cl. 757, 772-73 (2013). Consequently, the judgment denied the petitioner compensation.

The Federal Circuit affirmed this judgment. The basis for the affirmance was the finding that the petitioner had failed to establish an appropriate timing. Koehn, 773 F.3d at 1243-44. This is the holding of the Federal Circuit. Godfrey v. Sec'y of Health & Human Servs., No. 10-565V, 2015 WL 4972882 at *4-5 (Fed. Cl. Aug. 19, 2015) (granting motion for review for additional consideration of Koehn).

However, with respect to Althen prong 1, the Federal Circuit panel split. Two members stated "the Special Master committed several errors in the assessment of the first and second Althen prongs." Id. at 1243. The majority expanded on their reasoning in a footnote, stating "Had the Special Master

properly evaluated the evidence, we believe the Special Master would have likely found that Koehn met her burden under the first Althen prong." Id. at 1244 n.1.[24]

In the case at hand, Ms. McGuire relies upon this footnote. Pet'r's Preh'g Br. at 19-20 n.12. However, the views of the panel majority expressed in the footnote are dicta and do not constitute a holding requiring that all special masters credit any theory relying upon the Pinto article. See Highmark, Inc. v. Allcare Health Mgmt. Sys., Inc., 701 F.3d 1351, 1354 n.2 (Fed. Cir. 2012) (en banc) (per curiam) (discussing what panel opinions constitute binding precedent); see also Bristol-Meyers, 769 F.3d at 1353 (Taranto, J.) (dissenting from denial of reh'g en banc) ("[S]tatements in opinions must be read in context, considering their role in the decision and the facts of the case. Nevertheless, advocates often ignore this principle, relying on phrases and sentences found through database word searches without reading the whole opinion, and arguing for a precedential effect that is unwarranted."); Godfrey, 2015 WL 4972882 at *7 ("the circuit's criticisms of the special master's decision in Koehn with regard to causation are dicta").

Even if the footnote in Koehn were not dicta, however, it is unclear whether the views of the panel majority in that case could determine the outcome in Ms. McGuire's case. A "special master's task is to make a factual determination of causation based on the evidence in a particular case. A study of many individual cases may be useful evidence as to causation, but it does not compel the finder of fact to find causation in a particular case." Lampe v. Sec'y of Health & Human Servs., 219 F.3d 1357, 1366 (Fed. Cir. 2000). The mandate to consider the evidence in each case carries particular force because the evidence in Koehn differs from the evidence in this case.

Concededly, Ms. McGuire's theory shares the basic structure of the theory advanced in Koehn: the HPV vaccine induces the production of cytokines and the produced cytokines cause a disease. But, the theory in Ms. McGuire's case adds the step of crossing the blood brain barrier. The blood brain barrier is not trivial. In evaluating a theory, special masters may consider whether petitioners have presented a reliable basis for finding that a vaccine, which is administered in the body's periphery, can cause adverse effects in the part of the body protected by the blood brain barrier. See Moberly, 592 F.3d at 1324; Taylor v. Sec'y of Health &

[24] The remaining member of the panel did not believe that the errors regarding prong 1 and prong 2 presented "adequate grounds for reversal given the highly deferential standard of review." Koehn, 773 F.3d at 1245 (Moore, J., concurring).

Human Servs., 108 Fed. Cl. 807, 819 (Fed. Cl. 2013) (denying motion for review because, in part, petitioner failed to present evidence of a breach in the blood brain barrier).

In addition, the evidence surrounding the theory in Ms. McGuire's case differs from the evidence surrounding the theory in Koehn. For example, in this case, the Secretary presented the 2012 IOM report that found no evidence that cytokines cause a disease. Exhibit D, tab 4 (Stratton) at 76 [pdf 3]. This evidence was not offered in Koehn.

Another difference between Ms. McGuire's case and Koehn is the disease afflicting the petitioner. In Koehn, the disease was a form of arthritis. Here, the disease is chronic headaches. While in Koehn two members of the Federal Circuit appeared to conclude that the petitioner's evidence supported a finding that cytokines cause a type of arthritis, their conclusion would not necessarily mean that cytokines can cause headaches.

In this case, a finding that the HPV vaccine can cause chronic headaches depends upon the evidence introduced in this case. Althen, 418 F.3d at 1281. For the reasons discussed above, the Secretary has controverted Ms. McGuire's evidence to such a degree that the evidence does not preponderate in Ms. McGuire's favor on this point.

II. Timing

Although timing is the third factor from Althen, it is easier to assess the evidence immediately after the discussion of the theory. The causal theory largely influences the amount of time that is consistent with an inference of causation. Langland v. Sec'y of Health & Human Servs., 109 Fed. Cl. 421, 434 (2013).

As part of her case-in-chief, the petitioner bears the burden of establishing that the onset of her disease occurred within an acceptable time. Bazan v. Sec'y of Health & Human Servs., 539 F.3d 1347, 1352 (Fed. Cir. 2008). This formulation implies that the third prong from Althen actually contains two parts. First, there must be a showing that a range of time is "acceptable" to infer causation. Second, there must be a showing that the petitioner's disease arose in this acceptable time. Shapiro v. Sec'y of Health & Human Servs., 101 Fed. Cl. 532, 542-43 (2011), recons. denied after remand on other grounds, 105 Fed. Cl. 353 (2012), aff'd per curiam, 503 F. App'x 952 (Fed. Cir. 2013).

For Ms. McGuire, there is no dispute about the second part of the third prong. The time when her headaches arose was determined in the Revised Findings: sometime between October 25 and October 28, 2007. Because she received the first dose of the HPV vaccine on September 20, 2007, the interval between vaccination and onset of headaches for Ms. McGuire is 35 to 38 days. Consequently, her burden is to establish that approximately 38 days is an acceptable period for inferring causation.

With respect to the first part of the timing prong, the parties presented relatively little evidence. Actually, Ms. McGuire failed to present any opinion from Dr. Weig regarding the appropriate temporal interval until after an order directed her to review Dr. Weig's first two reports. Order, issued Dec. 15, 2014. His ensuing written opinion regarding the appropriate temporal relationship relied upon a 1994 report from the Institute of Medicine. Exhibit 40 at 1. In his oral testimony, Dr. Weig again cited the 1994 IOM report and the Prakash and Shaw article. Tr. 199-202.

The 1994 IOM report found that acute disseminated encephalomyelitis (ADEM) and Guillain-Barré syndrome (GBS) "generally occur after an interval of 5 days to 6 weeks following . . . injection of antigen." Exhibit 40, tab B (Kathleen Stratton et al., Adverse Events Associated with Childhood Vaccines: Evidence on Causality, Institute of Medicine (1994)) at 47. ADEM and GBS are demyelinating conditions. Tr. 265. Special masters have found the period of 5 days to 6 weeks is an acceptable interval for diseases mediated through an autoimmune process such as molecular mimicry. Lilly v. Sec'y of Health & Human Servs., No. 09-31V, 2009 WL 3320518, at *3 (Fed. Cl. Spec. Mstr. Sept. 28, 2009).

A problem for Ms. McGuire is that she did not present any evidence that suggests the time for a demyelinating disease matches the time for cytokines to produce headaches. Dr. Weig conceded that TNF is "not [causing] an autoimmune attack in the way that that term is typically used, which would mean like an attack to destroy . . . cells or myelin." Tr. 283. An admission that the process Dr. Weig has advanced involving TNF differs from the process of demyelination essentially makes an analogy to the 1994 IOM unpersuasive.

As discussed in the preceding section, Dr. Weig's theory contains at least three steps, beginning with the production of TNF in response to the vaccine. However, even for this foundational step, Dr. Weig did not know how long the body takes to produce pathogenic levels of cytokines. Tr. 265. Dr. Weig's inability even to estimate the time required casts doubt on his opinion regarding timing.

Dr. Swidan provided little assistance. She asserted that TNF in the serum might remain elevated during a chronic migraine attack. Tr. 546. But, in the Rozen and Swidan experiment, the TNF levels in serum was the same in controls and in people suffering headaches. The more meaningful substance is the cerebrospinal fluid. See Tr. 462 (Dr. Swidan noting that pharmacologists study whether a substance crosses the blood brain barrier). For the cerebrospinal fluid, Dr. Swidan acknowledged that there are no studies measuring TNF in the cerebrospinal fluid during a chronic migraine. Tr. 546. In addition, Dr. Swidan did not provide any testimony about the time required to produce TNF initially.

Questions were also posed to Dr. Saxon about the duration of cytokines. He stated that on the intracellular level, which is the relevant metric, most cytokines "work in minutes" and they last for hours. Tr. 690-91. If Dr. Saxon is correct, then Ms. McGuire would need to show that the short duration of cytokines is consistent with an onset of her headaches approximately 35 days later. See Koehn, 773 F.3d at 1244 (holding that special master was not erroneous in finding that a cytokine-driven reaction would not explain an onset approximately 60 days later).[25]

In commenting upon the appropriate temporal relationship, Dr. Saxon emphasized the weakness in the underlying theory. Dr. Saxon stated that Dr. Weig's theory for how the HPV vaccine can cause headaches "doesn't fit with any logic principles." "[B]ecause [the theory] doesn't fit an immunologic paradigm," "you don't need immunologic time frames." Tr. 645.

This criticism fits. Dr. Weig offered a theory involving cytokines, but his testimony revealed that he did not know the time needed to produce cytokines or the duration of cytokines. Therefore, Dr. Weig could not persuasively offer an explanation of the temporal interval that would be appropriate. His resort to the 1994 IOM appears to be a desperate reach for a straw. Ms. McGuire has not established the temporal interval between the HPV vaccination and the onset of

[25] As discussed in section I.C. above, the Federal Circuit's holding in Koehn was to rule the special master's analysis on timing was not arbitrary or capricious. Ms. McGuire would have been better served to pay attention to this analysis because the latency between the vaccination and the onset of headaches was multiple weeks, which is similar to the period of latency for arthritis in Koehn.

If Ms. McGuire's reliance on Koehn to establish prong one were correct, then it would seem to follow that Ms. McGuire would also be bound by Koehn on prong three.

chronic headaches that is appropriate for causation. Therefore, she has not established Althen prong three.

III. Logical Sequence of Cause of Effect

Because Ms. McGuire has not presented a persuasive theory explaining how the HPV vaccine can cause chronic headaches (prong 1) and she has not established the appropriate temporal relationship (prong 3), it follows, as a matter of logic, that she cannot establish "a logical sequence of events" beginning with the vaccination and ending with her chronic headaches. Caves, 100 Fed. Cl. at 134. Nevertheless, the evidence most closely related to this prong is also discussed to demonstrate that the entire record has been considered.

The Federal Circuit has identified several factors that may be probative with respect to the petitioner's burden on the second prong. These include, among other things, the opinions of a petitioner's treating physicians, expert testimony, challenge-rechallenge, and pathological markers. See Capizzano, 440 F.3d at 1322.

A. Treating Doctors

The order for briefs before hearing instructed Ms. McGuire to identify statements of treating doctors in which they expressed an opinion that the HPV vaccine caused Ms. McGuire's headaches. Order, issued Jan. 15, 2015. In response, Ms. McGuire identified seven doctors. Pet'r's Preh'g Br. at 34-36. However, as Ms. McGuire conceded during the pre-trial conference, in most of the quoted passages, the doctor is presenting only a chronological account of events. A sequence is not the same as a statement of causation. Cedillo v. Sec'y of Health & Human Servs., 617 F.3d 1328, 1347-48 (2010); La Londe v. Sec'y of Health & Human Servs., 110 Fed. Cl. 184, 206 (2013), aff'd on other ground, 746 F.3d 1334 (Fed. Cir. 2014); Langland v. Sec'y of Health & Human Servs., 109 Fed. Cl. 421, 439 (2013) (stating that the special master was not arbitrary in finding that the records from treating doctors "reflect no more than intake histories or temporal associations"); Caves, 100 Fed. Cl. at 127.

When these reports are set aside, Ms. McGuire is left with few useful statements from treating doctors. The potentially most useful statement comes from Dr. Herzog, the endocrinologist who saw Ms. McGuire nearly three years after the HPV vaccination. Dr. Herzog stated that "headache is reported as quite common after [Gardasil] vaccination (11-12%) but long lasting headache is unusual. . . . In the absence of response to standard migraine and muscle tension

headache treatments, the possibility of an immunologically mediated process could be considered." Exhibit 13 at 13.

On its face, Dr. Herzog's report that he could consider an immune mediated process a "possibility" does not satisfy the preponderant evidence standard. Paterek v. Sec'y of Health & Human Servs., 527 F. App'x 875, 879 (Fed. Cir. 2013). In addition, as Dr. Weig acknowledged on cross-examination, Dr. Herzog looked for evidence of immune-mediated diseases such as lupus that could have caused headaches as a consequence of that disease but did not find any evidence of an immune-mediated process. Tr. 267. Thus, Dr. Herzog's report does not lend much assistance to the theory that the HPV vaccine caused Ms. McGuire's primary headaches.

After Dr. Herzog's report, Dr. Levy's 2009 report received the most attention at the hearing. To recap, Dr. Levy practices alternative medicine and he saw Ms. McGuire on January 15, 2009, which was approximately two years after her headaches became permanent. According to the history Dr. Levy received, Ms. McGuire "never had headaches before the HPV vaccination." Exhibit 12 at 5. He stated that "It seems reasonable that there is a causal connection. Headache is a known side effect of HPV vaccine but studies show its frequency is similar in controls and vaccinees." Id.[26] He recommended various non-traditional interventions.

An initial problem with Dr. Levy's report is that the history he obtained is not accurate. Before the vaccination, Ms. McGuire did have at least one headache. See Tr. 412-13. An incorrect history may lead a doctor to incorrect reasoning. See Paterek, 527 F. App'x at 884 (holding that special master was not arbitrary in rejecting the opinion of a doctor who obtained an inaccurate history).

Another issue is that Dr. Levy practices, according to Dr. Weig, "alternative medicine." Tr. 268. No information suggests that Dr. Levy has sufficient expertise in either immunology or neurology to explain in a reliable fashion how the vaccine can lead to headaches. See Tr. 268-69.

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[26] Dr. Levy took the additional step of postulating that the immune system, including "proinflammatory cytokines," might affect the "trigemino-vascular system." He cited three articles. Exhibit 12 at 5. However, neither party submitted those articles.

These two points weaken the value of Dr. Levy's opinion that there is a causal connection between the HPV vaccination and Ms. McGuire's headaches. In addition, Dr. Levy's statement must be considered in the context of the many other doctors who knew Ms. McGuire received the first dose of her HPV vaccination before she started having recurring headaches in October 2007, but did not suggest that the vaccination caused the headaches. See 42 U.S.C. § 300aa–13(a)(1) (stating that special master must consider the record as a whole). From this perspective, Dr. Levy's opinion appears to be one not shared by his colleagues in the medical profession.

B. Rechallenge

The Federal Circuit recognizes "rechallenge" as a factor that may be relevant to considering whether a logical sequence of events supports the claim that a vaccine caused an injury. Capizzano, 440 F.3d at 1322 (finding that a re-challenge means "a patient who had an adverse reaction to a vaccine suffers worsened symptoms after an additional injection of the vaccine"); see also Tr. 650.

In accord with the Federal Circuit's instruction regarding rechallenge, petitioners who demonstrate rechallenge may prevail in the Vaccine Program. Hall v. Sec'y of Health & Human Servs., No. 02-1052V, 2007 WL 3120284, at *7-8 (Fed. Cl. Spec. Mstr. Sept. 12, 2007). However, petitioners must actually establish that they fulfill the challenge-rechallenge paradigm. Shapiro v. Sec'y of Health & Human Servs., No. 99-552V, 2012 WL 273686, at *12 (Fed. Cl. Spec. Mstr. Jan. 10, 2012), recons. denied after remand on other grounds, 105 Fed. Cl. 353 (2012), aff'd per curiam, 503 F. App'x 952 (Fed. Cir. 2013); Nussman v. Sec'y of Health & Human Servs., No. 99-500V, 2008 WL 449656, at *9-10 (Fed. Cl. Spec. Mstr. Jan. 31, 2008), mot. for rev. denied, 83 Fed. Cl. 111 (2008).

The reverse of challenge-rechallenge is challenge-dechallenge. "Dechallenge" refers to a situation in which removing the agent that supposedly incites an adverse reaction leads to an improvement. Rider v. Sandoz Pharm. Corp., 295 F.3d 1194, 1199-200 (11th Cir. 2002); Glastetter v. Novartis Pharm. Corp., 252 F.3d 986, 990 (8th Cir. 2001). If removing the allegedly harm-causing agent does not help, then the agent may not have actually caused the injury.

In this case, Ms. McGuire claims "challenge-rechallenge" and, at the same time, the Secretary has invoked "challenge-dechallenge." These disparate arguments are based upon different aspects of Ms. McGuire's medical history.

A succinct chronology to highlight only the events relevant to the challenge-rechallenge-dechallenge arguments begins with Ms. McGuire's receipt of the first dose of the HPV on September 20, 2007. Exhibit 1 at 88-89. Her headaches began between October 25 and October 28, 2007, and became constant one week later. Revised Findings, issued Oct. 12, 2012. On November 14, 2007, Ms. McGuire received the second dose of the HPV vaccine. Exhibit 1 at 86. The parties do not dispute these events.

The parties, however, contest the next event in this sequence. To support her argument in support of rechallenge, Ms. McGuire asserts that approximately two weeks after receiving the second dose, her headaches became worse. See Tr. 204-05 (Dr. Weig's testimony).[27] The Secretary does not agree with the contention that Ms. McGuire's headaches worsened about two weeks after the second dose. See Tr. 416-18 (Dr. Alexander). Different portions of the medical records support each party's interpretation. See exhibit 1 at 80 (Ms. McGuire reported on December 10, 2007, that "her headache has progressively worsened"); exhibit 1 at 54 (Ms. McGuire told her neurologist on March 20, 2008, that there "was no change in her headache after the second vaccine.")

Determining whether Ms. McGuire's headaches truly worsened at the end of November or beginning of December 2007 is not necessary for this decision. Even if her headaches did worsen, the worsening would not necessarily be a result of the November 14, 2007 vaccination. This is because for CDH, "there are good times and there are bad times." Tr. 417. In other words, the severity of the headaches fluctuates for a variety of unknown reasons. Thus, the possibility of worsening does not point, even on a more-likely-than-not standard, to the vaccine as the cause of any worsening. Thus, Ms. McGuire's reliance on the challenge-rechallenge theory is not persuasive.

This leaves the Secretary's challenge-dechallenge argument. Ms. McGuire and her experts maintain that the HPV vaccine provoked the production of an excessive amount of TNF, which, in turn, caused the headache. Part of Ms. McGuire's support for the assertion that high amounts of TNF cause headaches is the Prakash and Shaw study, which reported that people with headaches who

[27] Although Ms. McGuire presented the challenge-rechallenge argument through Dr. Weig, Ms. McGuire did not raise this contention in her pre-trial brief.

received high doses of steroids, which counter the production of TNF, improved. Exhibit 40 (Dr. Weig report) at 1; Pet'r's Preh'g Br. at 18.

From this foundation, the Secretary argues that Ms. McGuire does not fulfill the challenge-dechallenge paradigm. See Resp't's Preh'g Br. at 22-23. In May 2008, Ms. McGuire received a course of steroids. Exhibit 1 at 41, 46-47. However, the steroids either did not affect Ms. McGuire or they made her worse. Exhibit 12 at 3; exhibit 13 at 1; exhibit 3 at 66, 70-71. Dr. Saxon and the Secretary, thus, conclude that the lack of improvement indicates that TNF was not responsible for Ms. McGuire's headaches. Exhibit D at 11, Resp't's Preh'g Br. at 23.

Ms. McGuire effectively rebutted the Secretary's reliance on challenge-dechallenge. She showed that the amount of steroids used in the Prakash and Shaw study exceeded by a large margin the amount of steroids prescribed to Ms. McGuire. Tr. 196-98. Whether a stronger dose of steroids could have improved Ms. McGuire's headaches is uncertain and the dosages used by Prakash and Shaw are not typically prescribed. Tr. 687.

Overall, neither Ms. McGuire's challenge-rechallenge argument nor the Secretary's challenge-dechallenge is particularly persuasive.

C. Expected Response

A final way to consider whether Ms. McGuire presented preponderant evidence that the sequence of events logically points to the vaccine as the cause for her headaches is to evaluate whether she responded in a way predicted by her expert's theory. Both the Federal Circuit and the Court of Federal Claims have accepted this method of analysis. Hibbard v. Sec'y of Health & Human Servs., 698 F.3d 1355, 1364 (Fed. Cir. 2012); Dodd v. Sec'y of Health & Human Servs., 114 Fed. Cl. 43, 57 (2013) (special master did not err in finding that the facts of the vaccinee's injury did not fit the theory offered by the petitioner); La Londe v. Sec'y of Health & Human Servs., 110 Fed. Cl. 184, 205 (2013) (special master did not err in rejecting the petitioner's argument regarding prong 2 when the medical records did not support the theory being offered), aff'd, 746 F.3d 1334 (Fed. Cir. 2014).

Here, Dr. Weig wrote that the vaccinations produced "a state of chronic CNS inflammation with resulting headache." Exhibit 28 at 4; accord Tr. 246. People suffering from inflammation in their brains – as the term inflammation is usually used – have "confusion, seizures, aphasia, coma, cranial nerve palsies, CSF

pleocytosis, or systemic signs of inflammatory disease with fevers, elevated sedimentation rate." Exhibit A (Dr. Alexander's report) at 12-13. Furthermore, inflammation would be evident on MRIs and CT scans. Dr. Alexander was quite blunt in rejecting Dr. Weig's assertion that Ms. McGuire had inflammation in her central nervous system. Dr. Alexander stated that "there is not a shred of evidence that she has chronic CNS inflammation producing headaches." Id. at 12. At the hearing, Dr. Weig, essentially, agreed that Ms. McGuire did not have any of the signs or symptoms of CNS inflammation as conventionally understood. See Tr. 178, 246, 289, 708-09. In his rebuttal testimony, Dr. Weig acknowledged that his use of the term "inflammation" "would not correspond to the standard definition of the term . . . in the general medical community." Tr. 708.

Rather, Dr. Weig introduced a concept that was not discussed in his reports. He stated that Ms. McGuire suffered from "sterile inflammation." Tr. 177. Dr. Weig said that "sterile" means "there's no evidence of inflammatory cells in the spinal fluid." Tr. 177-78. Dr. Saxon clarified that Dr. Weig's "sterile inflammation" occurs at the molecular level. Tr. 604.

It would help a petitioner to show "evidence in the record suggesting that the proposed mechanism was at work" in her case. Moberly, 592 F.3d at 1324. But, this type of showing appears not to be possible because doctors do not routinely order cerebrospinal fluid to be tested for TNF. See exhibit 30 (Dr. Weig) at 5; Tr. 550. Thus, Ms. McGuire is unable to present any evidence that she reacted in a way that Dr. Weig's theory would predict.

Overall, Ms. McGuire's evidence regarding prong 2 was not of sufficient quality or persuasiveness to compensate for the deficiencies in prongs 1 and 3. Taken as a whole, Ms. McGuire did not meet her burden of proof on this prong.

Conclusion

Ms. McGuire claimed that the HPV vaccine caused her to suffer headaches and presented evidence, including opinions from Dr. Weig and Dr. Swidan, to support her allegation. However, the evidence does not preponderate in her favor.

The Clerk's Office is instructed to enter judgment in accord with this decision.

IT IS SO ORDERED.

s/ Christian J. Moran
Christian J. Moran
Special Master